

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/EP2004/009055

International filing date (day/month/year)
12.08.2004

Priority date (day/month/year)
13.08.2003

International Patent Classification (IPC) or both national classification and IPC
C12P21/00, C07K14/56

Applicant
SANDOZ AG

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

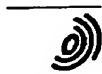
If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
- a. type of material:
- ☒ a sequence listing
- ☐ table(s) related to the sequence listing
- b. format of material:
- ☒ in written format
- ☒ in computer readable form
- c. time of filing/furnishing:
- ☐ contained in the international application as filed.
- ☐ filed together with the international application in computer readable form.
- ☒ furnished subsequently to this Authority for the purposes of search.
3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2004/009055

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
☒ claims Nos. 13,20-23 (all completely),14-19 (all partially)

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the whole application or for said claims Nos. 13,20-23 (all completely),14-19 (all partially)
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
- | | |
|----------------------------|--|
| the written form | <input type="checkbox"/> has not been furnished |
| | <input type="checkbox"/> does not comply with the standard |
| the computer readable form | <input type="checkbox"/> has not been furnished |
| | <input type="checkbox"/> does not comply with the standard |
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2004/009055

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:
- ☐ paid additional fees.
 - ☐ paid additional fees under protest.
 - ☒ not paid additional fees.
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
- ☒ not complied with for the following reasons:
- see separate sheet**
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☐ all parts.
 - ☒ the parts relating to claims Nos. 1-12 (all completely), 14-19 (all partially)

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-12 (all completely), 14-19 (all partially)
	No: Claims	
Inventive step (IS)	Yes: Claims	1-12 (all completely), 14-19 (all partially)
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-12 (all completely), 14-19 (all partially)
	No: Claims	

2. Citations and explanations

see separate sheet

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/EP2004/009055

Re Item IV.

Lack of unity of invention

The separate inventions/groups of inventions are:

1-12 (all completely), 14-19 (all partially)

A process to release a recombinant polypeptide of interest from the periplasm of the host cells by applying an osmotic shock directly on the host cells in the fermentation medium.

13, 20-23 (all completely), 14-19 (all partially)

A process for the purification of a recombinant interferon alpha 2 from a crude preparation of interferon alpha 2 by applying a specific sequence of several chromatographic steps as defined in claim 13 (i) to (v).

They are not so linked as to form a single general inventive concept (Rule 13.1 PCT) for the following reasons:

The subject matter of independent claim 1 is a process to release a recombinant polypeptide of interest from the periplasm of the host cells by applying an osmotic shock directly on the host cells in the fermentation medium. The problem to be solved is the provision of a simplified method to extract polypeptides from the periplasm of fermented procaryotes.

The subject matter of independent claim 13 is a process for the purification of a recombinant interferon alpha 2 from a crude preparation of interferon alpha 2 by applying a specific sequence of several chromatographic steps as defined in claim 13 (i) to (v). The problem to be solved is the provision of a simplified method to purify interferon alpha 2. The present set of claims solves two different, independent technical problems, which were known in the prior art. No technical relationship can be identified between the solutions to both problems, i.e. both solutions can be used independently from each other, their functioning does not depend on each other. Two different solutions to two different, known problems were put in a row. Additionally, independent claims 1 and 13 do not share a common matter. Therefore, they form different inventions.

As a consequence, the ISA is of the opinion that there is no single inventive concept

underlying the plurality of claimed inventions of the present application in the sense of rule 13.1 PCT. Consequently there is lack of unity and the different inventions, which are directed to the two above-mentioned technical problems, not belonging to a common inventive concept, are formulated as the different subjects on the communication pursuant to Art. 17(3)(a) PCT.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following document:

D1: HART R A ET AL.: BIOTECHNOLOGY, NATURE PUBLISHING CO. NEW YORK, US, vol. 12, November 1994 (1994-11), pages 1113-1117, ISSN: 0733-222X

1 Novelty (Art. 33(2) PCT)

The subject matter of claims 1 to 12 and 14 to 19 (as far as applicable) is a process to release a recombinant polypeptide of interest from the periplasm of the host cells by applying an osmotic shock directly on the host cells in the fermentation medium. Such a method has not been disclosed in the prior art. Therefore, the subject matter of claims 1 to 12 and 14 to 19 (as far as applicable) are novel under Art. 33(2) PCT.

2 Inventive Step (Art. 33(3) PCT)

D1 is the closest prior art and discloses the release of periplasmic IGF-I into the fermentation medium using chaotrope and reductant (urea, DTT, eachI + NaOH, see abstract), from which the subject matter of the present application differs in that the release of the periplasmic protein is achieved by an osmotic shock. No technical effect can be seen that is caused by said difference. The problem to be solved is the provision of an

alternative method to release the periplasmic protein of interest into the fermentation medium.

No hint can be identified in the prior art to apply an osmotic shock directly on cells in the fermentation broth. All osmotic shocks in the prior art were applied on harvested cell which were separated from the fermentation broth. The solution of the present application has the advantage that said harvesting step is not necessary and the whole procedure is simplified. Therefore, the present application involves an inventive step under Art. 33(3) PCT.

4 Industrial Application (Art. 33(4) PCT)

The present claims fulfill the requirement of industrial applicability (Art. 33(4) PCT).

5 Clarity (Art. 6 PCT)

Claims 1, 2, 14 and 15 attempt to define the subject matter in terms of the result to be achieved which merely amounts to a statement of the underlying problem. The technical features necessary for achieving this result should be added (Guidelines 5.35).